How Should Renal Hemodynamic Data Be Indexed in Obesity?[1]

Roland E. Schmieder, Alfred H. Beil, Horst Weihprecht, and Franz H. Messerli[2]

R.E. Schmieder, A.H. Beil, H. Weihprecht, Department of Internal Medicine-Nephrology, University of Erlangen-Nürnberg, Germany

F.H. Messerli, Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, LA

(J. Am. Soc. Nephrol. 1995; 5:1709–1713)

ABSTRACT

Clearance data are customarily indexed to body surface area of 1.73 m^2. This study examined whether this standard procedure gives correct values for renal perfusion in obese subjects. In 215 subjects who varied in age, gender, height, weight, obesity, and mean arterial blood pressure, RPF was determined by measuring the clearance of (^{131}I)*para*-aminohippuric acid. Multiple regression analysis of the whole study group revealed that age (β = −0.44, $P < 0.001$), height (β = +0.25, $P < 0.01$), and arterial blood pressure (β = −0.19, $P < 0.01$) were independent predictors of RPF, but that weight or body mass index was not. When related to body surface area, RPF appeared to decline with increasing obesity as follows: normal weight, 609 ± 153 mL/min per 1.73 m^2; overweight, 572 ± 149 mL/min per 1.73 m^2; severely overweight, 530 ± 145 mL/min per 1.73 m^2 ($P < 0.012$). In contrast, RPF related to height reflected a pattern concordant with the multiple regression analysis: normal weight, 3.76 ± 0.9 mL/min per meter; overweight, 3.86 ± 1.0 mL/min per meter; and severely overweight, 3.86 ± 1.0 mL/min per meter (not significant). A separate repetition of the whole analysis for both normotensive (N = 55) and hypertensive subjects (N = 160) revealed a result similar to that found for the whole group. Thus, our results show that obesity was not a determinant of RPF, and when related to body surface area, inappropriately low values of RPF were calculated for obese patients. It was concluded that RPF values correlate with height and not with surface area in obese subjects.

Key Words: *RPF, GFR, body size, body surface area, obesity, height, blood pressure*

[1] Received June 20, 1994. Accepted October 31, 1994.

[2] Correspondence to Dr. F.H. Messerli, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121.

1046-6673/0509-1709$03.00/0
Journal of the American Society of Nephrology

Ever since Homer W. Smith (1) established the use of a body surface area of 1.73 m^2—a value derived by the Van Slyke group (2) more than half a century ago—it has been customary to index all clearance data to this value. The rationale to adjust clearance data for body size is to allow easy comparison in subjects with different body weights and heights. Body surface area, which takes into account both weight and height, can be calculated with a nomogram originally presented by Dubois and Dubois (3). Because body surface area increases or decreases with weight gain or loss, respectively, renal hemodynamic data adjusted to body surface area of 1.73 m^2 will vary in patients whose weight is not stable, although no deterioration or improvement of renal function has been documented to take place. Hence, customary indexing of hemodynamic data to body area might be misleading in obese subjects.

Although it seems that there is a need for correcting GFR and RPF by a measure of body size, the question arises as to whether the current approach of adjusting RPF by body surface area is still adequate. This study was designed to address this question.

METHODS

Study Population

The study group comprised 215 white subjects of various age (13 to 74 yr), height (1.50 to 1.99 m), weight (47 to 136 kg), obesity (body mass index, 17.6 to 45.9 kg/m^2), and mean arterial pressure (71 to 157 mm Hg) at rest. Mean age was 40 ± 12 yr; average body mass index was 27.4 ± 5.0 kg/m^2. Of the 215 subjects, 157 were male and 58 were female; 55 were considered to be normotensive, and 160 were considered to have essential hypertension (62 to have borderline and 98 to have established essential hypertension) (World Health Organization [WHO] Stages I and II). The grouping was done according to WHO criteria by three or four casual blood pressure readings assessed on two different occasions. Subjects either were not receiving any cardiovascular medication or treatment was discontinued at least 4 wk before the invasive study and blood pressure measurements. Subjects did not follow any dietary guidelines.

Study subjects were enrolled if clinical and extensive laboratory investigations showed completely normal results and if secondary hypertension had been ruled out as well as WHO Stage III of hypertensive disease. Exclusion criteria were therefore advanced hypertensive fundoscopic changes, evidence of coronary artery disease, congestive heart failure (New York Heart Association Classes II to IV), previous cerebrovascular event, and any evidence of hepatic or renal insufficiency. In particular, electrocardiographic exercise stress testing, fundoscopic evaluation, chest x-ray and two-dimensional echocardiography were performed. Echocardiographic evidence of left ventricular hypertrophy or mild proteinuria was found in some subjects (WHO Stage II). Women were neither pregnant or lactating nor taking any hormonal contraceptive medication. The protocol was ap-

proved by our clinical investigation committee, and informed consent was obtained from each participant.

Study population was separated into three categories ("normal weight," "overweight," or "severe overweight") according to the classification used in the National Health and Nutrition Examination Surveys II (4). For men, the "overweight" category was defined as body mass index (weight in kilograms divided by height in meters squared) ≥ 27.8 and "severely overweight" was defined as body mass index ≥ 31.1. For women, these cutoff points were 27.3 and 32.3, respectively. These criteria can easily be compared with other standard mortality data (5). In 129 normal weight subjects (height, 1.73 ± 0.10 m), 46 overweight subjects (height, 1.72 ± 0.11 m), and 40 severe overweight subjects (height, 1.74 ± 0.08 m), body surface area was estimated with the formula originally presented by DuBois and Dubois (6).

Hemodynamic Assessment

After being off cardiovascular drugs for at least 4 wk, subjects were studied in the hemodynamic laboratory of the Ochsner Clinic after an overnight fast. Systemic and renal hemodynamic measurements were assessed by methods previously reported in detail (7).

RPF was determined by measuring the single-injection clearance of *para*-aminohippuric acid (PAH) tagged with radioactive iodine-131. After a bolus injection of tagged PAH, blood samples were collected at 5, 10, 15, 20, 30, 40, 50, 60, and 70 min after injection. By applying the two-compartment model, RPF was calculated from the disappearance curve of iodine-[^{131}I]PAH (8,9). Of note, the single-injection technique may result in a slight but systematic overestimation of PAH clearance; most important, however, the single-injection technique determines RPF more reliably than do the clearance techniques that require urinary collections (10,11).

Statistics

All data were analyzed by SAS programs (12). Group data are expressed as mean ± 1 SD in the Text. Linear regression analysis (Pearson) and multiple regression analysis were applied to both the entire population and the subgroups of normotensive and hypertensive subjects. Because of the large number of patients, eight variables were entered. In the first step, the most significant determinants were identified; the second and subsequent steps identified determinants that were independent of the first and explained, in addition, some variance of the dependent parameter, *i.e.*, RPF.

RESULTS

To evaluate the determinants of RPF, the following three conventional analyses were applied to the data of our whole study population and to the normotensive and hypertensive subjects separately.

Linear Regression Analysis

In our first attempt to examine determinants of renal hemodynamics in the entire study population, we conducted a linear regression analysis. RPF correlated with age ($r = -0.53$, $P < 0.001$), height ($r = +0.33$, $P < 0.001$) and blood pressure ($r = -0.34$, $P < 0.001$). Body mass index ($r = 0.07$) did not correlate with RPF. In normotensive subjects, RPF was related to age ($r = -0.42$, $P < 0.001$) and height ($r = 0.32$, $P < 0.01$), and in hypertensive subjects, it was related to age ($r = -0.53$, $P < 0.001$), height ($r = +0.36$, $P < 0.01$), and mean arterial pressure ($r = -0.34$, $P < 0.001$). Body mass index did not correlate with RPF in normotensives ($r = 0.16$) or in hypertensives ($r = -0.02$).

Multiple Regression Analysis

To determine the most significant independent factors for RPF, a stepwise multiple regression analysis was used. Age, sex, height, weight, and mean arterial pressure were entered as potential determinants of RPF without assigning priority. Age evolved as the most powerful determinant of RPF ($\beta = -0.44$) and explained more than half of the RPF variance ($R^2 = 0.53$) in the 215 subjects we examined. Mean arterial pressure ($\beta = -0.19$) and height ($\beta = +0.25$) emerged as additional determinants, independent of age. Sex ($\beta = -0.04$, n.s.) and weight ($\beta = +0.10$, not significant) were not found to be independent determinants for RPF. When multiple regression analysis was repeated with age, height, sex, mean arterial pressure, and body mass index (instead of weight) as potential determinants for RPF, a nearly identical analysis was found (Table 1). Again, when the multiple regression analysis was repeated, neither body mass index nor weight emerged as an independent determinant of RPF (Table 1). Thus, similar to the linear regression

TABLE 1. Determinants for RPF (multiple regression analysis)

Parameter	Standard Correlation Coefficient	*P* Value	Multiple Correlation Coefficient R^2
Whole Study Group ($N = 215$)			
Age	−0.44	<0.001	0.53
Height	+0.25	<0.001	0.58
Mean arterial pressure	−0.19	<0.001	0.61
Body mass index	+0.09	NS[a]	—
Sex	−0.04	NS	—
Normotensive Subjects ($N = 55$)			
Age	−0.40	<0.001	0.45
Height	+0.36	<0.003	0.57
Mean arterial pressure	−0.14	—	—
Body mass index	+0.12	—	—
Sex	−0.06	—	—
Hypertensive Patients ($N = 160$)			
Age	−0.44	<0.001	0.53
Height	+0.25	<0.001	0.59
Mean arterial pressure	−0.16	<0.002	0.62
Body mass index	+0.05	NS	—
Sex	−0.03	NS	—

[a] NS, not significant.

analysis, the degree of obesity was not found to modulate renal perfusion.

Analysis of Variance

By using the conventional definition for obesity (see Methods), RPF was assessed in the normal weight, overweight, and severely overweight groups. Again, obesity was not a determinant of RPF: in normal-weight subjects, RPF was 640 ± 168 mL/min; in overweight subjects, it was 668 ± 189 mL/min; and in severely overweight subjects, it was 671 ± 188 mL/min.

In contrast, by applying the commonly used RPF/body surface area criteria to adjust RPF for body size, a significant fall in RPF with a rising degree of obesity was calculated: normal weight, 609 ± 153 mL/min per 1.73 m^2; overweight, 572 ± 149 mL/min per 1.73 m^2; severely overweight, 530 ± 145 mL/min per 1.73 m^2 ($P < 0.012$) (Figure 1).

When RPF/height criteria were used, no significant difference between these three groups was seen ($P > 0.20$): normal weight, 3.76 ± 0.9 mL/min per meter; overweight, 3.86 ± 1.0 mL/min per meter; and severely overweight, 3.86 ± 1.0 mL/min per meter (Figure 1). The latter result (RPF/height) was in accordance with the analysis of the uncorrected values. In reanalyzing the data for normotensive and hypertensive subjects separately, RPF, if related to body surface area, decreased significantly in the overweight and severely overweight subgroups compared with the normal-weight group (Table 2). In contrast, if RPF was adjusted to height, no significant difference between normal and overweight or severely overweight subjects was found, in either normotensive or hypertensive individuals.

DISCUSSION

Age, height, and blood pressure emerged as the most powerful determinants of RPF in this analysis of 215 subjects who varied in age, height, sex, arterial pressure, stage of hypertensive disease, and degree of obesity. Obesity (as measured by either weight or body mass index) *per se* was not found to influence RPF, in either normotensive or hypertensive subjects. Thus, a correction of RPF to body size by using RPF/body surface area criteria is not supported by our data. In contrast, height was a much stronger predictor of RPF, and RPF corrected for height corresponded more accurately to the pattern observed in the uncorrected values.

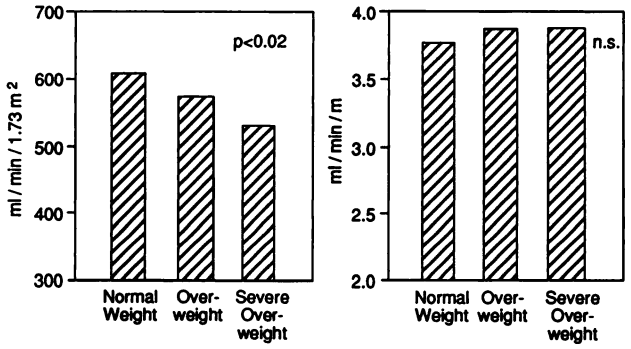

Figure 1. RPF adjusted to body size. If related to body surface area (left panel), a significant fall in RPF with rising body weight was calculated ($P < 0.012$). When using RPF/height criteria (right panel), no significant difference between these three groups was seen ($P > 0.20$). n.s., not significant.

A weight gain of 50 kg in a healthy 25-year-old man would lead to a "fall" in his RPF from 472 to 384 mL/min per 1.73 m^2 (assuming a normal RPF of 600 mL/min "unadjusted" RPF and calculating 2.2 and 2.7 m^2 of body surface area, respectively). Conversely, a weight loss of 50 kg will reduce his cardiovascular risk but is unlikely to cause his RPF to rise by more than 20%. However, this is exactly what using RPF/body surface criteria leads one to believe. A rise and fall in plasma flow parallel with changes in body weight have never been demonstrated. There are no clinical or experimental documents indicating that the kidney grows or shrinks after a respective increase or loss in body weight. Moreover, because the monitoring of renal function over time is important for the evaluation of renal disease, the indexing of renal dynamic data should be independent of changes in body weight. Normalizing RPF to height and not to body surface area appeared to be the most appropriate approach in taking into account changes in body weight.

Adjusting renal hemodynamic data to lean body weight appears to be an alternative approach. In patients with reduced renal function (creatinine clearance, 30 to 100 mL/min), the use of lean body weight instead of actual body weight clearly improves the prediction of creatinine clearance (13,14). In this study, we did not use lean body weight for adjusting RPF, because according to the mathematical equations, the only determinant of lean body mass is height (lean body weight for males [females] = 50 kg [45.5] + 2.3 kg/height in inches) (15). Hence, the results with lean body weight as a correcting factor were the same as those with height, but additional calculations were required.

Our data suggest, although do not prove, that similar considerations have to be made when adjusting GFR to body size. Bohle and coworkers (15) provided evidence that, in inflammatory and noninflammatory glomerular diseases, the excretory function of the glomeruli for substances usually eliminated with the urine is detrimentally affected by tubulointerstitial changes. Measured GFR appears to be strongly correlated with structural tubulointerstitial changes, thus being of great value for the control of disease progression by the clinician. Obesity *per se* has not been shown to impair tubulointerstitial integrity, and accordingly, GFR related to body surface area would lead to falsely low values. Similarly, correct values for RPF are essential, because the degree of the renal

TABLE 2. RPF adjusted to body surface area or body height in normotensive and hypertensive subjects

Parameter	Normal Weight	Overweight	Severely Overweight	*P* Value
Normotensive Subjects (*N* = 55)	*N* = 34	*N* = 10	*N* = 11	—
RPF (mL/min)	702 ± 135	608 ± 160	701 ± 131	NS[a]
RPF related to body surface area (mL/min per m^2)	392 ± 25	312 ± 82	320 ± 68	0.003
RPF related to height (mL/min per m)	4.12 ± 0.78	3.56 ± 0.99	4.07 ± 0.74	NS
Hypertensive Subjects (*N* = 166)	*N* = 102	*N* = 38	*N* = 26	—
RPF (mL/min)	642 ± 172	648 ± 183	621 ± 197	NS
RPF related to body surface area (mL/min per m^2)	344 ± 90	322 ± 78	280 ± 85	0.004
RPF related to height (mL/min per m)	3.69 ± 0.92	3.76 ± 0.96	3.54 ± 1.08	NS

[a] NS, not significant.

vascular involvement, either structural or functional, was found to be closely correlated with a reduction in RBF: the more severe histologic changes in the kidney, the more reduced was RBF (16–18).

A similar procedure for correcting echocardiographic left ventricular structural parameters by body surface area has recently been criticized (19). Adjusting left ventricular mass by body surface area allows obese persons higher thresholds of left ventricular hypertrophy. Thus, the upper normal value for the left ventricular mass/body surface area criteria is reached at a higher left ventricular mass than when uncorrected values are used. As a consequence, the cardiovascular risk from increased left ventricular mass in obese hypertensive patients is falsely underestimated (20). Levy and coworkers (19) showed that this "forgiveness" of obesity does not occur when left ventricular mass/height criteria are used. Hence, to quantify left ventricular hypertrophy in obese hypertensive patients, Levy *et al.* suggest using left ventricular mass/height criteria (19), thereby identifying the cardiovascular risk for obese subjects more precisely.

In conclusion, our data show that, by using RPF/body surface area criteria, obese persons would display inappropriately low values of RPF and would be misdiagnosed to have impaired renal perfusion. Therefore, we recommend using RPF/height criteria to correct RPF by a measure of body size. These considerations might be extended to adjusting GFR for body size.

REFERENCES

1. **Smith HW:** The Kidney. Structure and Function in Health and Disease. New York: Oxford University Press; 1951.
2. **McIntosh JF, Möller R, Van Slyke DD:** Studies of urea excretions. III. The influence of body size on urea output. J Clin Invest 1928;6:467, 496, 543.
3. **Du Bois D, Du Bois EF:** The measurement of the surface area of man. Arch Intern Med 1916;15:868–871.
4. **National Center for Health Statistics:** Plan and Operation of the National Health and Nutrition Examination Survey, 1976–1980. Washington, DC: U.S. Public Health Service; 1981—DHHS publication no. 81-1317. (Vital and Health Statistics Series 1, no. 15).
5. **Van Itallie TB:** Health implications of overweight and obesity in the United States. Ann Intern Med 1985;103: 983–988.
6. **Du Bois D, Du Bois EF:** Clinical colorimetry: Formula to estimate approximate surface area, if height and weight be known. Arch Intern Med 1916;17:33–39.
7. **Messerli FH, Decarvalho JGR, Christie B, Frohlich ED:** Systemic and regional hemodynamics in low, normal and high cardiac output borderline hypertension. Circulation 1978;58:441–448.
8. **Tauxe WN, Maher FT, Taylor WF:** Effective renal plasma flow: Estimation from the theoretical volumes of distribution of intravenously injected 131 I-orthioodo hippurate. Mayo Clin Proc 1971;46:524–531.
9. **Silkalns GI, Jeck D, Earon J, *et al.*:** Simultaneous measurement of glomerular filtration rate and renal plasma flow using plasma disappearance curves. J Pediatr 1973;83:749–757.
10. **Rosenbaum JL, Kramer MS, Raja RM, Manchanda R, Lazaro N:** Determination of inulin and p-aminohippurate clearances without urine collection. Nephron 1973; 10:347–359.
11. **Uhlmann W:** Zur Problematik der Totalclearance. Über den Zusammenhang von Plasmaspiegelabfall, renaler Ausscheidung, Verteilungsvorgang und Clearance von PAH nach einmaliger Injektion. Klin Wochenschr 1955; 33:713–719.
12. **SAS Institute Inc.:** SAS User's Guide. Statistics Version. 5th Ed. Cary, NC: SAS Institute Inc; 1985.
13. **Pesola GR, Akhavan I, Madu A, Shah NK, Carlon GC:** Prediction equation estimates of creatinine clearance in the intensive care unit. Intensive Care Med 1993;19:39–43.
14. **Devine B:** Gentamicin therapy. Drug Intell Clin Pharmacol 1974;8:650–655.
15. **Bohle A, Mackensen-Haen S, Von Gise H:** Significance of tubulointerstitial changes in the renal cortex for the excretory function and concentration ability of the kidney: A morphometric contribution. Am J Nephrol 1987; 7:421–433.
16. **Castleman B, Smithwick RH:** Relation of vascular disease to hypertensive state based on study of renal biopsies from 100 hypertensive patients. JAMA 1943;121: 1256–1261.
17. **Castleman B, Smithwick RH:** Relation of vascular disease to hypertensive state; adequacy of renal biopsy as determined from study of 500 patients. N Engl J Med 1948;239:729–732.
18. **Hollenberg NK, Epstein M, Basch RI, Merrill JP:** "No man's land" of the renal vasculature. An arteriographic and hemodynamic assessment of the interlobar and

arcuate arteries in essential and accelerated hypertension. Am J Med 1969;47:845–854.
19. **Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP:** Echocardiographically detected left ventricular hypertrophy: Prevalence and risk factors. Ann Intern Med 1988;108:7–13.
20. **Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH:** Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–352.